Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Inspection findings on Health Based Exposure Limits and Cross Contamination

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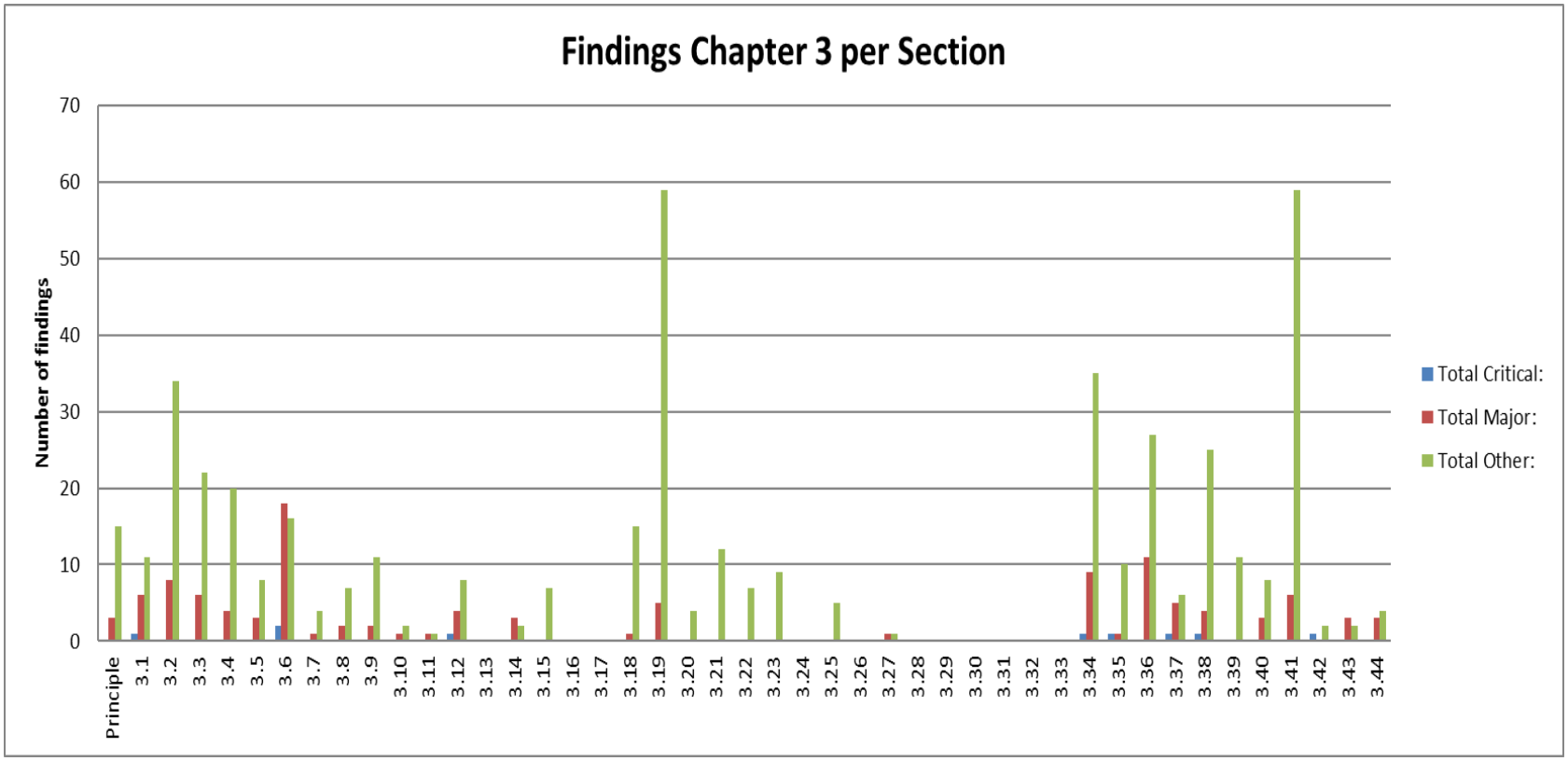
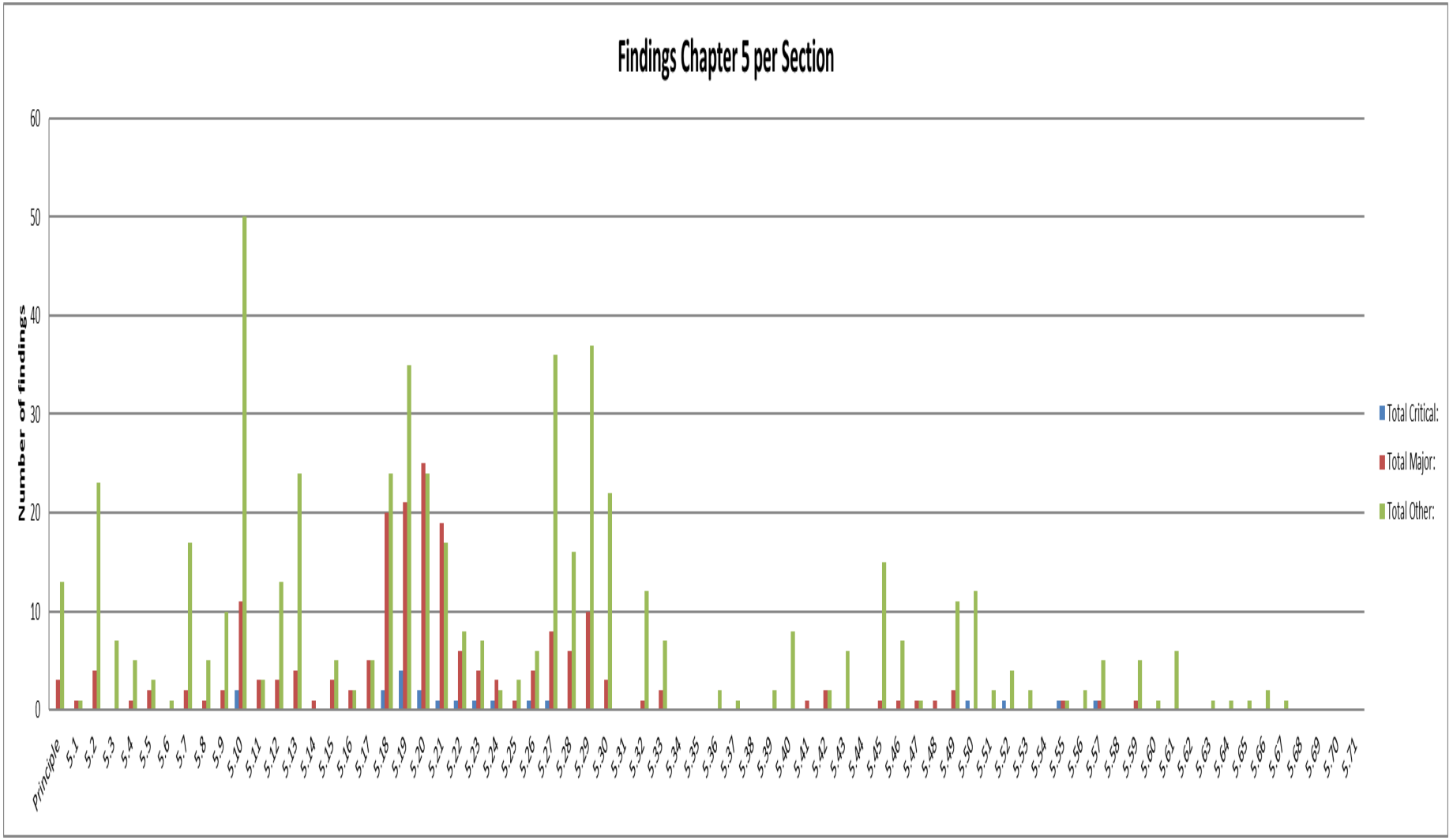
Content

- Some Metrics
- Key issues encountered
- Examples of deficiencies
- Key challenges for inspectors

Metrics 2016 (MHRA data)



Metrics 2016 (MHRA data)



Top 10 Most cited deficiency groups 2016

(MHRA data)

Ranking	Groups	Critical	Major	Others
1	Quality System	38	449	772
2	Sterility Assurance	34	190	162
3	Production	20	191	543
4	Complaints and Recall	11	80	110
5	Qualification/Validation	10	123	232
6	Premises & Equipment	9	113	464
7	Computerised Systems	9	44	120
8	Personnel	8	42	150
9	Documentation	2	166	646
10	Quality Control	2	42	192

Key Issues encountered

- Health based exposure limit guide or equivalent not applied – sites not taking toxicological hazards of products into consideration.
- No link between the health based exposure limits and the technical and organisational controls applied.
  - Sites regarding health based limits as cleaning limits without using these within a structured risk assessment.
  - No recorded alignment to a justified level of organisational and technical controls.

Key Issues encountered

- There is an overall lack of a structured approach to Health based limits:
  - No SOP on how to apply the HBEL guideline.
  - There is no document format for the assessment of data and the presentation of the results, meaning every assessment may have a different layout and structure.
  - The publications reviewed during HBEL assessment are not listed and assessments are recorded on 1-2 pages without any justification.
  - Companies ‘blindly’ buy these assessments from third parties without reviewing the content as they do not have staff with the necessary expertise.

Key Issues encountered

- Companies like to use the most easy way to calculate health based limits:
  - Often SHE department provides OEL-data to GMP
  - There are still companies which use the LD50 approach for calculating HBELs, with reference to PDA TR29 or APIC
  - SHE department and GMP department may work together, but GMP does not evaluate SHE knowledge from the GMP point of view.
- Cleaning validation conducted of manual cleaning operations provides minimal confidence that the cleaning process is validated on the basis it is used (by multiple operators).
- Visual inspection frequently fails – equipment predominantly clean but not fully visually clean.
  - Employees making decisions that equipment is ‘clean enough’ or ??
  - Not inspecting all high risk occluded surfaces.

Examples of deficiencies recorded

Example 1 – a company not using expert assessment

- 2.1 Risk Assessment and practices for the introduction of new molecules were deficient:-
- 2.1.1 Reviews of potential risks appear to be minimal using a literature search.
- 2.1.2 In several cases seen the documents available for review did not include all those listed in the SOP. No justification had been made for reduced coverage.
- 2.1.3 No comments had been made even though an MSDS held for _____ indicated that the product might cause mutations or disorders of a foetus.
- 2.1.4 Staff evaluating the health based data did not appear to have any medical or toxicological training.
- 2.1.5 The company have not carried out formal risk assessments of molecules handled at the site in accordance with document EMA/CHMP/CVMP/SWP/169430/2012.

Example 2 - a company that has made no assessment against the guide and is also weak on traditional approaches.

1.1.4 Systems to control Contamination and cleaning validation were deficient in that:

1.1.4.1 The company had not determined health based safety assessments and PDE values for products manufactured currently.

1.1.4.2 There was no system to assess new products introduced to site to ensure the hazards posed could be adequately controlled.

1.1.4.3 There was no process on site to assess the organisational and technical control measures required for products to ensure the risk of cross contamination was controlled.

1.1.4.4 There were no named restricted product classes that the company would process and systems were not adequately robust for higher hazard products.

1.1.4.5 Cleaning validation considered the worst case product on an annual basis rather than as new products were introduced.

1.1.4.6 Worst case evaluations did not trigger revalidation or review of a cleaning method where a higher toxicity or more potent product was introduced to site where the solubility in cleaning solvent was the same.

1.1.4.7 Although the cleaning validation SOP QA47 required annual revalidation, none had been performed since 2011.

1.1.4.9 In the 2011 study (_____) only two of the three cleaning validation batches were completed however the study was signed off as acceptable without any comment or justification.

1.1.4.10 Swab limits for the above study were set at a very high 12.34ug/ cm2 (1234 µg/dm2) a level which is often above the visual threshold of products (the visual threshold of the _____was not known by the company).

Example 3 – a company that has made no assessment against the guide and are not using any expert assessment

- Contamination control, evaluation and introduction of new molecules to the site was deficient, for example:-
- 2.1.1 Local evaluation of product introduction risks was limited to a preliminary assessment form attached to SOP QA 047.
- 2.1.2 The only comment made on the forms seen indicated that the products were non-sterile and no comments had been made about the potential risks of the molecules.
- 2.1.3 There was no requirement to evaluate key information sources to evaluate potential toxicological risks.
- 2.1.4 Staff carrying out the existing limited evaluation were QA staff and did not have sufficient medical or toxicological training.
- 2.1.5 The company have not started to evaluate health-based exposure limits in accordance with EMA/CHMP/CVMP/SWP/169430/2012.

Example 4 – a company yet to introduce any toxicological assessment

The technical and organisational measures to control risks of contamination and cross contamination were deficient as evidenced by:

2.1.1 The process used to assess and control cross contamination risks did not include a toxicological evaluation of the risks presented by the materials used in the manufacturing areas.

2.1.2 The cleaning procedures for sieves and fluid bed driers were deficient in that:

2.1.2.1 There was insufficient detail to ensure that the cleaning process would be undertaken consistently, for example there were no diagrams or photographs to identify difficult to clean areas.

2.1.2.2 There was no requirement for the equipment to be visually clean at the end of cleaning.

2.1.3 Screen 316 100# had not been cleaned before being stored and it was not possible to determine when the equipment was last used.

Example 5 - a company weak on practical controls

- No tools were deployed to assess whether equipment such as tote bins were visibly clean. The site utilised ambient room lighting without a light source or mirror, thus the assessment was not robust.
- Poor cleaning was a significant cross contamination risk as exemplified by product residues in the capsule filling machine even though this had been subjected to full cleaning on more than one occasion since its last use on .
- Dirty bulk containers were transferred to the Granulation washroom past stored clean containers without appropriate controls in place to prevent cross contamination of the clean units.

Example 6 - another company weak on practical controls

Technical and organisational measures to ensure the prevention of cross contamination were deficient as evidenced by:

2.1.1 Production cleaning processes were deficient as evidenced by:

2.1.1.1 Gross product contamination was observed in the transfer lines from the liquid formulation room to the holding vessels- despite these lines having been cleaned onthe 25th January 2016.

2.1.1.2 The procedure for washing and drying silo bins (IBCs) does not require a formal visual check for either cleanliness or dryness after processing.

Example 7 – a company not using risk management adequately and using dedication of a group of products as a key control without overall consideration of relative risks.

2.1 Cross contamination control was deficient and not aligned to the level of hazard posed by some

products, in that:

2.1.1 The company had not adequately assessed and confirmed the suitability of organisational and technical control measures for the hazards of products manufactured in the general products areas.

2.1.2 Although the company had established a high potency (TH) area they had not adequately confirmed the suitability of organisational and technical control measures to prevent cross contamination in that area. Although some additional cleaning steps had been incorporated in this area there was incomplete confidence over the equipment dismantling process and overall cross contamination prevention.

2.1.3 There was no procedure to define how cleaning methods should be developed requiring use of detailed equipment drawings, expert knowledge of the design/construction and plans to fully dismantle equipment as part of the cleaning development strategy.

2.1.4 The Risk Assessments (RA) conducted of the cross contamination risk did not challenge the controls in place at the time the RA was generated and referenced in the document but rather assumed they were effective.

2.1.5 The risk assessment approach did not consider failure modes within each of the system areas assessed e.g. opportunities for failure of manual operations.

2.1.6 There was no clear recorded requirement to raise an incident or deviation where visual inspection by second production personnel or QA personnel found residual product.

2.1.7 There was no record that lines related to vacuum extracts, used to remove airborne powders close to equipment, were cleaned between manufacture of different products, for example the vacuum unit used in the encapsulation area in the high potent TH area. It was noted by the inspector that a small portion of white powder was seen in the end of dust extract EME432.

Key challenges for the inspectors

- Inspectors typically do not have adequate toxicology experience/knowledge to enable an assessment of toxicological data in a PDE.
- Although these can be referred (in some agencies) to toxicologists for input this is atypical for inspections.
  - It adds an extra dimension of complexity for which regulators are not resourced.
  - It delays finalisation of findings and any required action.
- Some agencies have been unable to secure toxicological support for their inspectors.

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